



## The biology of influenza viruses

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### ABSTRACT

The influenza viruses are characterized by segmented, negative-strand RNA genomes requiring an RNA-dependent RNA polymerase of viral origin for replication. The particular structure of the influenza virus genome and function of its viral proteins enable *antigenic drift* and *antigenic shift*. These processes result in viruses able to evade the long-term adaptive immune responses in many hosts.

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### 1. The influenza viruses

The influenza A, B, and C viruses, representing three of the five genera of the family *Orthomyxoviridae*, are characterized by segmented, negative-strand RNA genomes. Sequencing has confirmed that these viruses share a common genetic ancestry; however, they have genetically diverged, such that reassortment—the exchange of viral RNA segments between viruses—has been reported to occur within each genus, or *type*, but not across types. Influenza A viruses are further characterized by the *subtype* of their surface glycoproteins, the hemagglutinin (HA) and the neuraminidase (NA). Influenza viruses have a standard nomenclature that includes virus type; species from which it was isolated (if non-human); location at which it was isolated; isolate number; isolate year; and, for influenza A viruses only, HA and NA subtype. Thus, A/Panama/2007/1999 (H3N2) was isolate number 2007 of a human influenza A virus taken in the country of Panama in 1999, and it has an HA subtype 3 and an NA subtype 2. While many genetically distinct subtypes—16 for HA and 9 for NA—have been found in circulating influenza A viruses, only three HA (H1, H2, and H3) and two NA (N1 and N2) subtypes have caused human epidemics, as defined by sustained, widespread, person-to-person transmission [1].

### 2. Virion structure and organization

By electron microscopy, influenza A and B viruses are virtually indistinguishable. They are spherical or filamentous in shape, with the spherical forms on the order of 100 nm in diameter and the filamentous forms often in excess of 300 nm in length. The influenza A virion is studded with glycoprotein spikes of HA and NA, in a ratio of approximately four to one, projecting from a host cell-derived lipid membrane [1]. A smaller number of matrix (M2) ion channels traverse the lipid envelope, with an M2:HA ratio on the order of one M2 channel per  $10^1$  to  $10^2$  HA molecules [2]. The envelope and its three integral membrane proteins HA, NA, and M2 overlay a matrix of M1 protein, which encloses the virion core. Internal to the M1 matrix are found the nuclear export protein (NEP; also called nonstructural protein 2, NS2) and the ribonucleoprotein (RNP) complex, which consists of the viral RNA segments coated with nucleoprotein (NP) and the heterotrimeric RNA-dependent RNA polymerase, composed of two “polymerase basic” and one “polymerase acidic” subunits (PB1, PB2, and PA). The organization of the influenza B virion is similar, with four envelope proteins: HA, NA, and, instead of M2, NB and BM2. Influenza C virions are structurally distinct from those of the A and B viruses; on infected cell surfaces, they can form long cordlike structures on the order of 500  $\mu$ m. However, influenza C virions are compositionally similar, with a glycoprotein-studded lipid envelope overlying a protein matrix and the RNP complex. The influenza C viruses have only one major surface glycoprotein, the hemagglutinin–esterase–fusion (HEF) protein, which corresponds functionally to the HA and NA of influenza A and B viruses, and one minor envelope protein, CM2 [1].

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**Table 1**

The genomic segments of influenza A/Puerto Rico/8/1934 (H1N1) virus and their encoded proteins

Segment	Segment length in nucleotides	Encoded protein(s)	Protein length in amino acids	Protein function
1	2341	PB2	759	Polymerase subunit; mRNA cap recognition
2	2341	PB1 PB1-F2	757 87	Polymerase subunit; RNA elongation, endonuclease activity Pro-apoptotic activity
3	2233	PA	716	Polymerase subunit; protease activity
4	1778	HA	550	Surface glycoprotein; major antigen, receptor binding and fusion activities
5	1565	NP	498	RNA binding protein; nuclear import regulation
6	1413	NA	454	Surface glycoprotein; sialidase activity, virus release
7	1027	M1 M2	252 97	Matrix protein; vRNP interaction, RNA nuclear export regulation, viral budding Ion channel; virus uncoating and assembly
8	890	NS1 NEP/NS2	230 121	Interferon antagonist protein; regulation of host gene expression Nuclear export of RNA

The PB2, PA, HA, NP and NA proteins are each encoded on a separate RNA segment. The M2 and NEP are both expressed from spliced mRNAs, while PB1-F2 is encoded in a +1 alternate reading frame (kindly provided by Megan L. Shaw).

### 3. Genome structure

The influenza A and B virus genomes each comprise eight negative-sense, single-stranded viral RNA (vRNA) segments, while influenza C virus has a seven-segment genome (see Table 1). The eight segments of influenza A and B viruses (and the seven segments of influenza C virus) are numbered in the order of decreasing length. In influenza A and B viruses, segments 1, 3, 4, and 5 encode just one protein per segment: the PB2, PA, HA and NP proteins. All influenza viruses encode the polymerase subunit PB1 on segment 2; in some strains of influenza A virus, this segment also codes for the accessory protein PB1-F2, a small, 87-amino acid protein with pro-apoptotic activity, in a +1 alternate reading frame [3]. No analogue to PB1-F2 has been identified in influenza B or C viruses. Conversely, segment 6 of the influenza A virus encodes only the NA protein, while that of influenza B virus encodes both the NA protein and, in a –1 alternate reading frame, the NB matrix protein, which is an integral membrane protein corresponding to the influenza A virus M2 protein [4]. Segment 7 of both influenza A and B viruses code for the M1 matrix protein. In the influenza A genome, the M2 ion channel is also expressed from segment 7 by RNA splicing [5], while influenza B virus encodes its BM2 membrane protein in a +2 alternate reading frame [6,7]. Finally, both influenza A and B viruses possess a single RNA segment, segment 8, from which they express the interferon-antagonist NS1 protein [8–10] and, by mRNA splicing, the NEP/NS2 [11,12], which is involved in viral RNP export from the host cell nucleus. The genomic organization of influenza C viruses is generally similar to that of influenza A and B viruses; however, the HEF protein of influenza C replaces the HA and NA proteins, and thus the influenza C virus genome has one fewer segment than that of influenza A or B viruses.

The ends of each vRNA segment form a helical hairpin, which is bound by the heterotrimeric RNA polymerase complex; the remainder of the segment is coated with arginine-rich NP, the net positive charge of which binds the negatively charged phosphate backbone of the vRNA [13–15]. Each vRNA segment possesses non-coding regions, of varying lengths, at both 3' and 5' ends. However, the extreme ends of all segments are highly conserved among all influenza virus segments; these partially complementary termini base-pair to function as the promoter for vRNA replication and transcription by the viral polymerase complex. The noncoding regions also include the mRNA polyadenylation signal and part of the packaging signals for virus assembly.

A segmented genome enables *antigenic shift*, in which an influenza A virus strain acquires the HA segment, and possibly the NA segment as well, from an influenza virus of a different sub-

type. This segment reassortment can happen in cells infected with different human and animal viruses, and the resulting virus may encode completely novel antigenic proteins to which the human population has no preexisting immunity. Pandemic influenza arises when antigenic shift generates a virus to which humans are susceptible but immunologically naïve. Antigenic shift likely produced the influenza A (H1N1) virus that was the causative agent of the 1918–1919 “Spanish flu,” whose lethality was unparalleled in modern times. Characterization of the reconstructed 1918 influenza virus indicated that its unique constellation of genes was responsible for its extreme virulence, with the HA, NA, and PB1 genes all contributing to its high pathogenicity [16,17]. The global spread of the pandemic was almost certainly enabled by the acquisition of antigenically novel surface proteins, to which much of the world's population was immunologically naïve [18].

### 4. The influenza virus replication cycle

#### 4.1. Virus attachment

Influenza viruses recognize *N*-acetylneuraminic (sialic) acid on the host cell surface. Sialic acids are nine-carbon acidic monosaccharides commonly found at the termini of many glycoconjugates. Thus, they are ubiquitous on many cell types and in many animal species. The carbon-2 of the terminal sialic acid can bind to the carbon-3 or carbon-6 of galactose, forming  $\alpha$ -2,3- or  $\alpha$ -2,6-linkages; these different linkages result in unique steric configurations of the terminal sialic acid. The sialic acid moiety is recognized and bound by the HA spikes on the surface of influenza viruses, which have a preferential specificity for either  $\alpha$ -2,3- or  $\alpha$ -2,6-linkages. In human tracheal epithelial cells,  $\alpha$ -2,6-linkages predominate, while  $\alpha$ -2,3-linkages are more common in duck gut epithelium. Sialic acids with terminal  $\alpha$ -2,3-linkages are also present in human respiratory epithelium, though in less abundance than those with  $\alpha$ -2,6-linkages [19,20]; consequently, humans and other primates can be infected by avian influenza viruses, albeit with overall less efficiency than by human strains [21–23].

The differential expression of sialic acids in the mammalian respiratory tract may help to explain the low infectivity but high pathogenicity of some avian strains. In humans,  $\alpha$ -2,3-linked sialylated proteins, while less abundant overall, are most prevalent in the lower respiratory tract (bronchioles and alveoli). The lungs are not as accessible to airborne virus particles as is the upper respiratory tract (nasopharynx, paranasal sinuses, trachea, and bronchi); so avian virus infection is relatively rare in humans. However, when avian strains do infect the human lung, a severe and rapidly pro-

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